AMENDMENTS TO THE SPECIFICATION

Please amend paragraphs [0001] - [0004] as follows:

[0001] Serotonergic and adrenergic receptors, functioning reciprocally in the central nervous and cardiovascular systems, are involved in the pharmacologic activities of some anti-depressants. It is well established that noradrenaline neurons modulate the activity of the 5-HT(serotonin, 5-Hydroxytryptamine) system and several lines of evidence support the theory that the 5-HT system influences brain noradrenaline neurons (Villalobos-Molina R, et al., *Eur. J. Pharmacol.*, 277:181-185,1995). Indeed, some selective or subtype-selective α_2-adrenoceptor blockers, such as yohimbine, rauwolscine, and phentolamine, have been shown to possess an affinity for 5-HT_{1A} receptors in the rat brain (Llado et al., 1996). Although α_2-adrenoceptor blockers may provide some protection in rats against bacterial lipopolysaccharide (LPS)-induced hyperglycemia, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), corticosteroid release, and mortality (Haskó G. et al., *J. Endocrinol.*, 144:457-462,1995 [[)]] ; Hirata Y. and Ishimaru S., *Clin. Sci.*, 103:332S-335S,2002), similar protective functions provided by anti-depressants with α_2-adrenoceptor and 5-HT blocking activities have not been investigated as thoroughly.

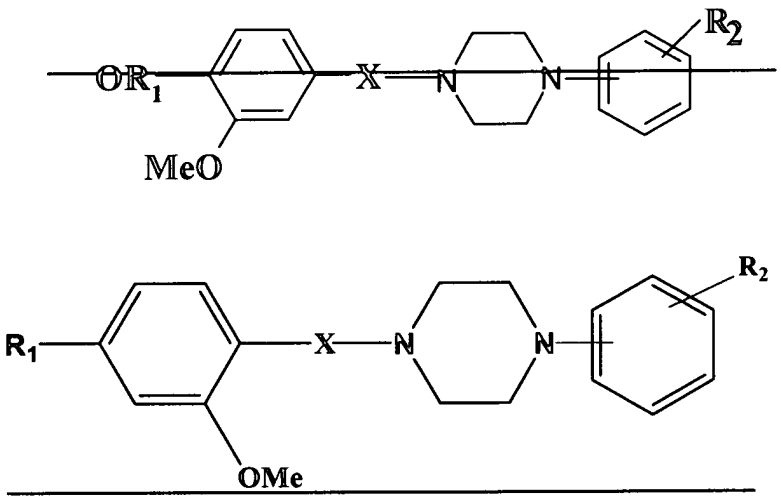
[0002] Lipopolysaccharide (LPS)-induced inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1) and interferon (IFN) could be regulated by blocking α_2-adrenergic receptors, which are involved in the balance between noradrenergic and serotonergic systems in central neurons (Shen Y. et al., *Life. Sci.*, 65:1773-1786, 1999). Despite the importance of LPS in inflammation, many aspects of LPS-induced dysfunction remain poorly

understood. To date, the relationship between LPS-induced hypotension and high mortality is un-resolved. LPS is known to affect cerebral neurotransmission. The ability of α_2-adrenoceptor blocking antidepressant treatment to attenuate LPS-induced-depression in rats has been cited as evidence that inflammatory cytokines play an important role in depression (Koyama, S. *Am. J. Physiol.*, 16:R665-R662, 1984 [[).]] ; Dunn AJ. and Swiergiel AH., *Neuroimmonomodulat.*, 9:163-169, 2001). It has been reported that selective blocking of α_2-adrenoceptors located on noradrenergic axon terminals resulted in an increase in the release of noradrenaline (Haskó et al., 1995). In *in vivo*, α_2- and ß-adrenoceptors on macrophages can be activated by the endogenous ligand noradrenaline, released from noradrenergic varicosities and by adrenergic drugs. It is suggested that these increases regulate LPS-induced production of cytokines (Szelenyi J, Kiss JP and Vizi ES., *J. Immunol.*, 103:34-40, 2000).

[0003] 2-Chlorphenyl-1-piperazinyl benzene (CPB) is a basic chemical structure, fuound in trazodone-like anti-depressants with α_2-adrenoceptor and 5-HT antagonist activities. Some ß-adrenoceptor blockers, such as pindolol, have been found to have nanomolar binding affinities for 5-HT_{1A} receptors and have prevented some 5-HT_{1A} receptor-mediated responses (Haddjeri N, de Montigny C, and Blier P., *Biol. Psychiat.*, 45:1163-1169, 1999). ß-adrenergic blocking agents with serotonergic properties have proved beneficial to depressed patients, notably those with myocardial infarction and congestive heart failure (Pitzalis MV. et al., *Am. Heart. J.*, 141:765-771, 2001); Valuck RJ. et al., *Dr. S.*, 10:511-516, 2001); Ko DT. et al., *JAMA.*, 288:351-357, 2002). Aryloxypropanolamines, and especially those which are isoeugenol-based

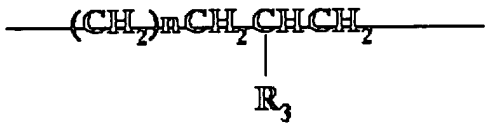
ones have been reported to have anti-oxidizing activities, in addition to their ß-adrenoceptor blocking effects (Aubriot S.et al., *Bioorgan. Med. Chem.*, 12:209-212, 1995 [[)]] ; Huang YC. et al., *Drug. Dev. Res.*, 47:77-89, ~~2001~~ 1999; Bioorg. Med. Chem. 9: 1739-1746, 2001). Trazodone, a well known anti-depressant, with 5-HT agonist/antagonist activity, 5-HT reuptake inhibition and adrenoceptor blocking activities, was taken as a reference to evaluate associated pharmacologic activities (~~Cohn~~ Cohen et al., 1983; Owens MJ.et al., *J. Pharmac. Exp. Ther.*, 283:1305-1322, 1997).

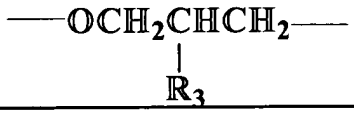
[0004] It is an object of the present invention to provide a compound having the formula I



(I)

where R_1 is alkyl group or alkenyl group; X represents

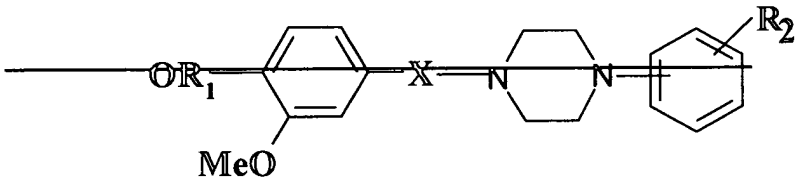


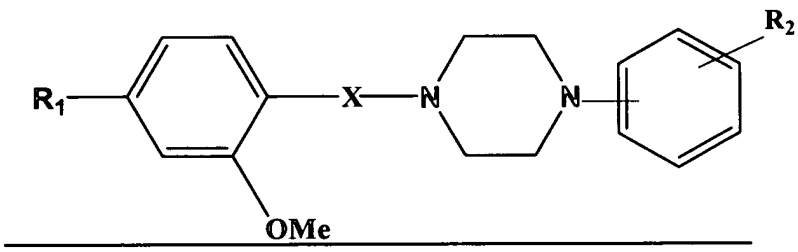


R_2 is selected from the group consisting of a halogen (o, m, p) group, $-NH_2$, $-NO_2$ and a hydrogen group; R_3 is a hydrogen group or OH; and n is 0 to 2. The halogen group is preferably F, Cl, Br or I. It is also an object to provide the isoeugenol derivative having pharmacologically α_2-adrenergic/5-HT_{2A} antagonist, 5-HT re-uptake inhibition, and anti-oxidant activities. It is further an object to provide a method of the compound.

Please amend paragraph [0006] as follows:

[0006] The compound is shown as formula I ,

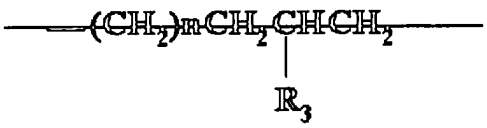




(I)

Where R_1 is alkyl group or alkenyl group;

X represents



;

R_2 is a halogen (o, m, p), $-NH_2$, $-NO_2$ or a hydrogen group, wherein the halogen is F, Cl, Br or I. R_3 present a hydrogen group or OH; and n is 0 to 2. Epichlorohydrin was mixed with isoeugenol and NaOH dissolved in ethanol, boiled to reflux for 2-6 hours. ~~Obtained mixture was removed t~~ [[T]]he included ethanol was removed from the mixture, and the mixture is ~~and~~ passed through silica gel column chromatography, eluated with n-hexane and ethyl acetate, dried with reduced pressure and obtained ~~4-epoxy isoeugenol~~ 4-oxy-methyloxirane-3-methoxy-1-propylenyl benzene. Piperazine was dissolved in methanol, mixed with ~~4-epoxy isoeugenol~~ 4-oxy-methyloxirane-3-methoxy-1-propylenyl benzene to reflux at 100°C for 2-6 hours. Obtained mixture was then removed the included methanol by reduced pressure using vacuum pump. The residue was passed through silica gel column chromatography, eluated with n-hexane and ethyl

acetate, dried by reduced pressure, and crystallized with methanol to obtain white crystal of compound.

Please amend paragraph [0021] as follows:

[0021] Intra-cisternal injections of KMST (0.3, 0.03 μmol), yohimbine [0.03 μmol), and clonidine (38 pmol), were performed in rats as described by ~~Dyan~~ Duan et al (1987). Briefly, rats weighing 250-300 g were anaesthetized with pentobarbital sodium (50 mg kg^{-1}, i.p.) and mounted in a David-Kopf stereotaxic instrument (Yeh JL. et al., *Brain. Res. Bull.*, 30:641-648, 1993). The calvarium was exposed and a 1 mm diameter trephine hole was drilled 1.8 mm lateral to the coronary and 1.5 mm posterior to the sagittal sutures. A cannula (0.7 mm O.D.) connected to a Hamilton syringe (RN-705, 5051) by PE-50 was advanced 4.7 mm into the brain using the electrode carrier.

Please amend paragraph [0026] as follows:

[0026] Inhibition of 5-HT reuptake was measured by slight modification of the method of Hatanaka K. et al. (Neuropharmacology., 35:1621-1626, 1996) and ~~Diga M.~~ Helmeste et al. (Life. Sci., 62:2203-2208, 1998). Wistar rats weighting 150-200 g were decapitated, the cerebral cortex or striatum was dissected and crude synaptosomes were prepared. The crude synaptosomes were suspended in about 16 mg wet tissue per 1 ml of Krebs buffer for 5-HT uptake. Uptake was initiated by the addition of 50 μl of [^{3}H] 5-HT to give a final concentration (30 nM), continued for 2 min at 37°C, and terminated by cooling the mixture in an ice bath. Saline was added to the

incubation mixture, which was then filtered through a Whatman GF/B glass filter under reduced pressure. To determine nonspecific uptake, incubation was performed at 0°C.

Please amend paragraph [0028] as follows:

[0028] The scavenging ability of the test compounds on aqueous peroxyl radicals was determined by the method described by T[[a]]suchiya M. et al. (Methods Enzymol., 213:460-472, 1992). The stoichiometric factors of the test compounds with hydrophilic peroxyl radicals were calculated by the equation as mentioned Ascorbic acid was used as a positive control.

Please amend paragraph [0054] as follows:

[0054] 1-(3-chlorphenyl-1-piperazinyl)-2-propanol-3-oxy-(2-methoxy-4-~~propylenyl~~ propenyl)-benzene or 1-((2-methoxy-4-~~propylenyl~~ propenyl) -phenoxy)-3 -((3-chlorphenyl-piperazinyl)-2-propanol (1).

Please amend paragraph [0055] as follows:

[0055] 3-chlorophenyl piperazine (5g) was dissolved in metnanol (20 ml), mixed with ~~4-epoxy isocugenol~~ 4-oxy-methyloxirane-3-methoxy-1-propylenyl benzene (20g), and boiled to reflux at 80 °C for 4 hours. Obtained mixture was then removed the included methanol by reduced pressure using vacuum pump. The residue was passed through silica gel colum chromatography, eluated with n-hexane and ethyl acetate (9:1), dried by reduced pressure, and crystallized with methanol to obtain 13.8g white crystal of compound 2. 1-((2-methoxy-4-~~propylenyl~~

propenyl)-phenoxy)-3-((3-chlorphenyl-piperazinyl)-2-propanol (1).

Please amend paragraphs [0057]-[0058] as follows:

[0057] 1-((4-chlorphenyl-1-1piperazinyl)-2-propanol-3-oxy)-(2-methoxy-4-~~propylenyl~~ propenyl)-benzene or 1-((2-methoxy-4-~~propylenyl~~ propenyl)-phenoxy)-3-((4-chlorphenyl-piperazinyl)-2-propanol (2).

[0058] 4-chlorophenyl piperazine (5 g) was dissolved in metnanol (20 ml), mixed with ~~4-epoxy isoeugenol~~ 4-oxy-methyloxirane-3-methoxy-1-propylenyl benzene (20 g), and boiled to reflux at 80 °C for 4 hours. Obtained mixture was then removed the included methanol by reduced pressure using vacuum pump. The residue was passed through silica gel colum chromatography, eluated with n-hexane and ethyl acetate (9:1), dried by reduced pressure, and crystallized with methanol to obtain 16.3 g white crystal of compound 2.

Please amend paragraph [0060] as follows:

[0060] 1-(3-chlorphenyl-1-piperazinyl)-propyloxy-2-methoxy-4-~~propylenyl~~ propenyl-benzene or 1-((2-methoxy-4-~~propylenyl~~ propenyl)-phenoxy)-3-((3-chlorphenyl-piperazinyl)-propane (3).